PCT/EP 00/08190

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10-069280

EP 00/08190

4

Bescheinigung | Certificate | Attestation

Die angehefteten Unterlagen stimmen mit der ursprünglich eingereichten Fassung der auf dem nächsten Blatt bezeichneten europäischen Patentanmeldung überein.

The attached documents are exact copies of the European patent application described on the following page, as originally filed.

Les documents fixés à cette attestation sont conformes à la version initialement déposée de la demande de brevet européen spécifiée à la page suivante.

Patentanmeldung Nr. | Patent application No. | Demande de brevet n°

99202710.2

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

I.L.C. HATTEN-HECKMAN

DEN HAAG, DEN
THE HAGUE,
LA HAYE, LE 13/12/00

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Blatt 2 der Bescheinigung
Sheet 2 of the certificate
Page 2 de l'attestation

Anmeldung Nr.:
Application no.:
Demande n°: 99202710.2

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Date of filing:
Date de dépôt: 23/08/99

Anmelder:
Applicant(s):
Demandeur(s):
DUPHAR INTERNATIONAL RESEARCH B.V
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NETHERLANDS

Bezeichnung der Erfindung:
Title of the invention:
Titre de l'invention:
Phenylpiperazines as serotonin reuptake inhibitors

In Anspruch genommene Priorität(en) / Priority(ies) claimed / Priorité(s) revendiquée(s)

Staat: State: Pays:	Tag: Date: Date:	Aktenzeichen: File no. Numéro de dépôt:

Internationale Patentklassifikation:
International Patent classification:
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Am Anmeldetag benannte Vertragstaaten:
Contracting states designated at date of filing: AT/BE/CH/CY/DE/DK/ES/FI/FR/GB/GR/IE/IT/LI/LU/MC/NL/PT/SE/[redacted]
Etats contractants désignés lors du dépôt:

Bemerkungen:
Remarks:
Remarques:
The original title f the application reads as follows:
New phenylpiperazines.

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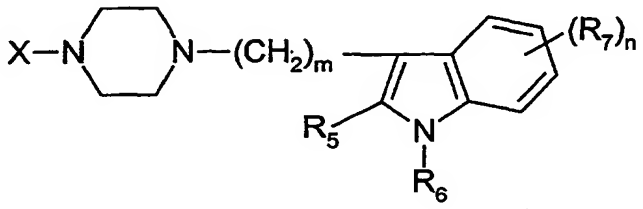
New phenylpiperazines

(67)

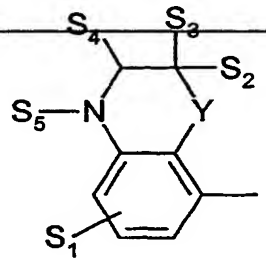
The invention relates to a group of novel phenylpiperazine derivatives of the formula (I):



(I)

wherein:

- X is 1) a group of the formula

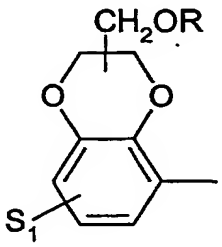


(1)

wherein

- S_1 is hydrogen or halogen,
- S_2 and S_3 are independently hydrogen, alkyl (1-6C), phenyl or benzyl,
- S_4 represents two hydrogen atoms or an oxo group,
- S_5 is H or alkyl (1-4C), and
- Y is C, O or S,

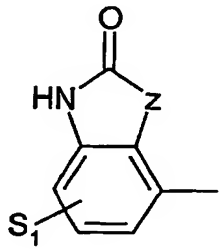
or 2) a group of the formula



(2)

wherein S_1 has the above meaning and R is H, alkyl (1-4C), alkoxyalkyl (2-6C), alkenyl (2-4C) or alkynyl (2-4C),

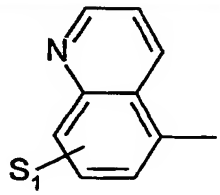
or 3) a group of the formula



(3)

wherein S_1 has the above meaning and Z is C, O or N,

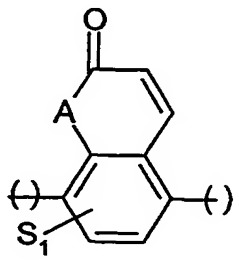
or 4) a group of the formula



(4)

wherein S_1 has the above meaning,

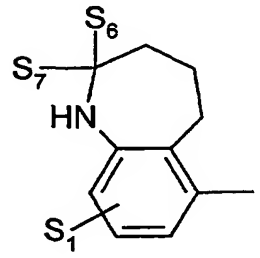
or 5) a group of the formula



(5)

wherein S_1 has the above meaning and A is O or N, linked to the piperazine ring with position 5 or 8,

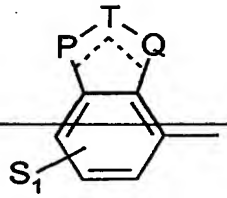
or 6) a group of the formula



(6)

wherein S_1 has the above meaning and S_6 and S_7 represent hydrogen atoms or an oxo group,

or 7) a group of the formula



(7)

wherein one of the dotted lines can represent a double bond, S_1 has the above meaning, and

P=T=Q=nitrogen

or P=T=nitrogen and Q=C

or P=Q=nitrogen and T=C or C-CH_3

or P=nitrogen, and T and Q are carbon

or P=nitrogen, T is carbon and Q is sulphur

- m has the value 2 to 6;
- n has the value 0-2;
- R_5 and R_6 are independently H or alkyl (1-3C); or R_5+R_6 represent a group $-(CH_2)-_p$ wherein p has the value 3-5, and
- R_7 is alkyl (1-3C), alkoxy (1-3C), halogen or cyano; or R_6+R_7 represent a group $-(CH_2)_q$ wherein q has the value 2-4,

and salts thereof, which show high affinity for the dopamine D_2-receptor and are good serotonin reuptake inhibitors (SRI's).

Preferred compounds of the invention are compounds having formula (I) wherein X represents a group of the formula (1), (2) or (3), wherein the symbols have the meanings given above and the salts thereof.

Especially preferred are compounds having formula (I) wherein X is the group with the formula (1) wherein S_1=H, S_2=CH_3, S_3=H, S_4=oxo, S_5=H and Y is oxygen, m is 3, R_5=R_6=hydrogen, n is 0 or 1 and R_7 is fluoro,
and the salts thereof.

It has been found that the compounds according to the invention show high affinity for both the dopamine D_2 receptor and the serotonin reuptake site. This combination is useful for the treatment of schizophrenia and other psychotic disorders which enables a more complete treatment of all disease symptoms (e.g. positive symptoms and negative symptoms).

However, some of the compounds having formula (I) show partial agonist activity at dopamine receptors making them particularly suitable for the treatment of Parkinson's disease.

The compounds show activity as antagonists at dopamine D_2 receptors as they potentially antagonize apomorphine-induced climbing behaviour in mice. The compounds also show activity as inhibitors of serotonin reuptake, as they potentiate 5-HTP induced behaviour in mice.

The compounds are active in therapeutic models sensitive to clinically relevant antipsychotics (e.g. the conditioned avoidance response; Van der Heyden & Bradford, Behav. Brain Res., 1988, 31:61-67) and antidepressants or anxiolytics (e.g. suppression of stress-induced vocalization; van der Poel et al., Psychopharmacology, 1989, 97: 147-148).

In contrast to clinically relevant dopamine D_2 receptor antagonists the described compounds have a low propensity to induce catalepsy in rodents and as such are likely to induce less extrapyramidal side effects than existing antipsychotic agents.

The inhibitory activity of serotonin reuptake inherent in these compounds may be responsible for the therapeutic effects observed in behavioural models sensitive to either antidepressants or anxiolytics.

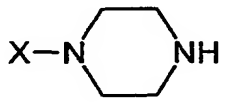
The compounds can be used for the treatment of affections or diseases of the central nervous system caused by disturbances in either the dopaminergic or serotonergic systems, for example: aggression, anxiety disorders, autism, vertigo, depression, disturbances of cognition or memory, Parkinson's disease, and in particular schizophrenia and other psychotic disorders.

Pharmacologically acceptable acids with which the compounds of the invention can form suitable acid addition salts are for example hydrochloric acid, sulphuric acid, phosphoric acid, nitric acid, and organic acids such as citric acid, fumaric acid, maleic acid, tartaric acid, acetic acid, benzoic acid, p-toluene sulphonic acid, methanesulphonic acid and naphthalene sulphonic acid.

When the compounds comprise a centre of chirality both the racemic mixture and the individual enantiomers belong to the invention.

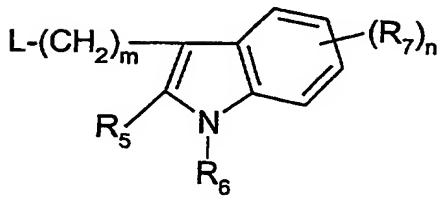
The compounds and their acid addition salts can be brought into forms suitable for administration by means of suitable processes using auxiliary substances such as liquid and solid carrier materials.

The compounds having formula (I) can be prepared by reaction of a compound of the formula



(II)

under basic conditions with a compound of the formula

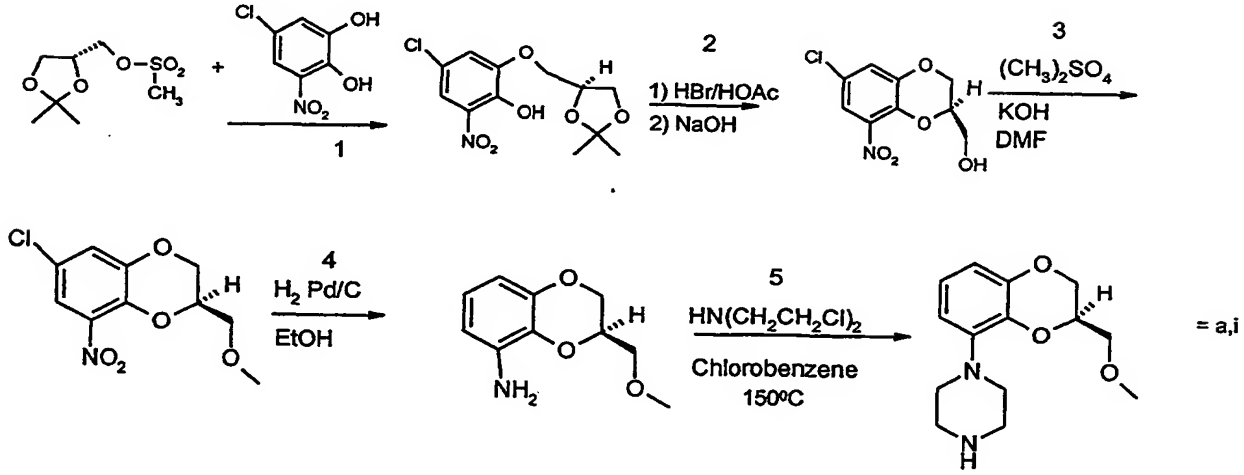


(III)

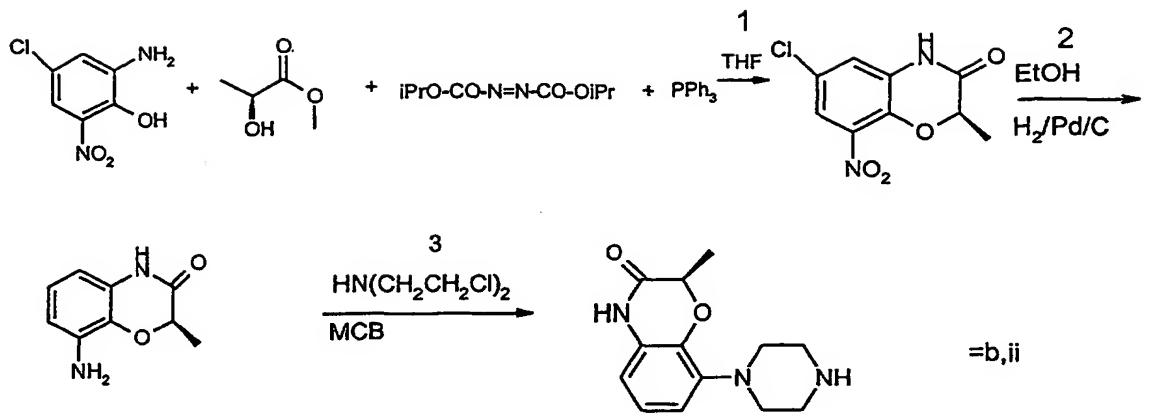
in which formulae the symbols have the meanings given above, and L is a so-called leaving group such as a halogen atom or a mesylate group.

The piperazine compounds having formula (II) can be obtained as described in EP 0138280, EP 0189612 and/or EP 0900792, or in an analogous manner.

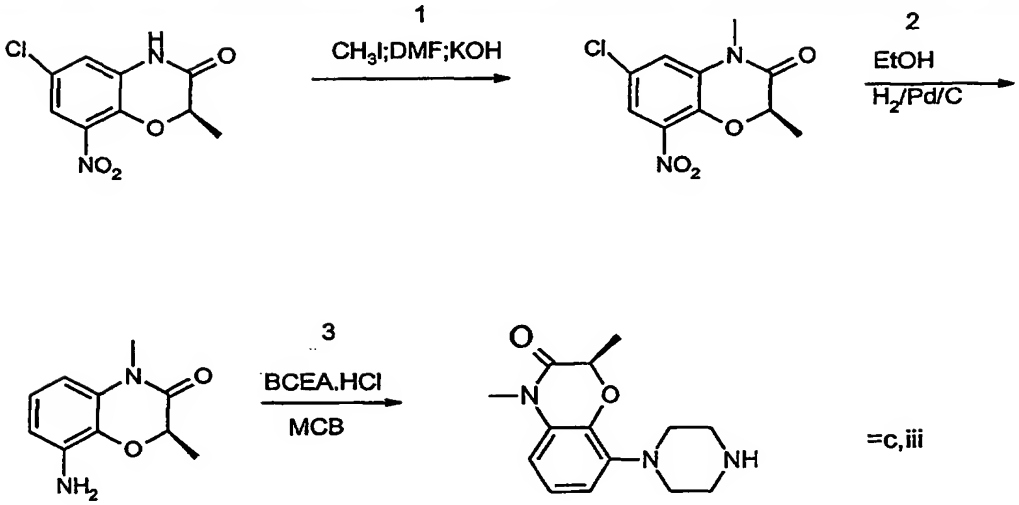
The preparation of the piperazines having formula (II) can be carried out as indicated in schemes (i)-(iv) below. Some of the routes result in optically pure piperazine derivatives.



Scheme (i)



Scheme (ii)



Scheme (iii)

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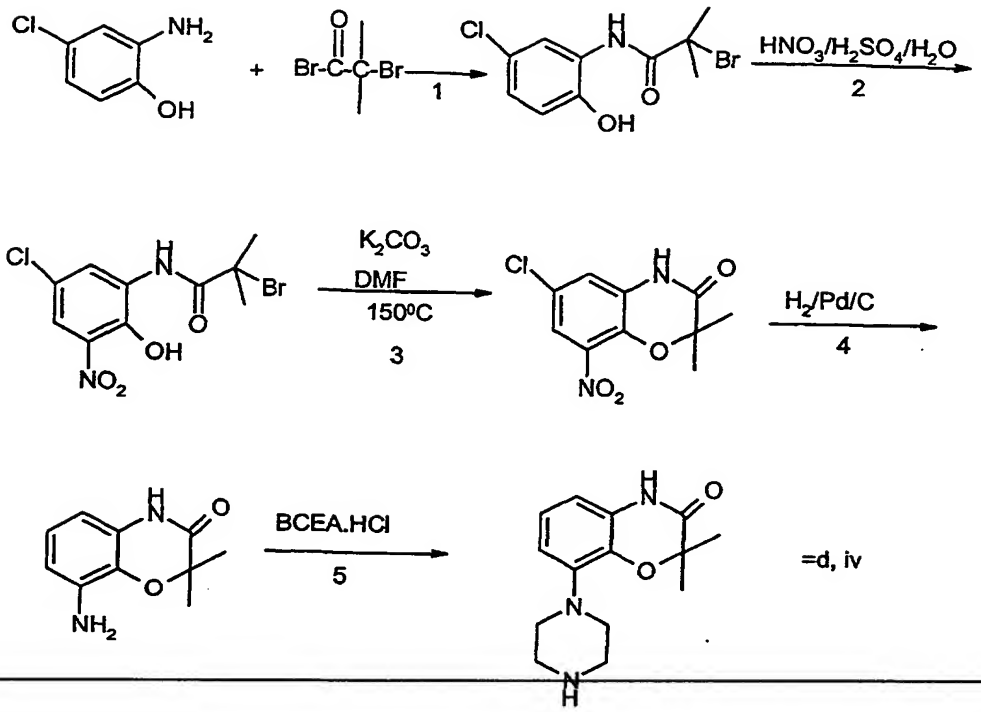


Scheme (iv)

The starting compounds having formula (III) can be prepared according to methods known for analogues compounds, as described for example in Organic Process Res. and Dev. 1997 (1), 300-310.

The invention will now be illustrated by means of the following Examples:

Example 1: preparation of compound a.i (see scheme i)

Step 1 (scheme i): To a solution of chloronitrocatechol (6.45 g , 34 mmol) in dry DMSO (50 ml) was added powdered NaOH (2.72 g , 68 mmol). After stirring for 30 minutes a solution was added of R-glycerolketal mesylate (8.0 g, 38 mmol) in DMSO (20 ml) and this mixture was heated at 80°C during 24 hours. After cooling to room temperature the reaction mixture was poured into water (200 ml), acidified with 1N HCl and extracted with methyl t-butylether. The organic fraction was washed with water and dried on $MgSO_4$. After removal of the drying agent and the solvent *in vacuo*, the resulting oil was subjected to flash chromatografy (SiO_2, eluent PE/aceton=3/1). Yield 9.29 g (90%) of the S-ketal.

Step 2 (scheme i): To a solution of the S-ketal (31 g, 102 mmol) in acetic acid (120 ml) was added 35% HBr in acetic acid (80 ml) and this mixture was rotated for 2 hours on a rotavapor in a waterbath of 50°C. The reaction mixture was diluted with ethanol (96%, 250 ml), cooled in a salt/ice mixture and then NaOH (50% in water, 250 ml) was added slowly, keeping the temperature below 15°C. After adding ethanol (250 ml) and water (250 ml) the reaction mixture was stirred at room temperature for 16 hours. Then concentrated HCl (about 300 ml) and water were added and the mixture extracted with ethyl acetate. After washing the organic fraction with 5% $NaHCO_3$ (4x500 ml), the solvent was removed *in vacuo* and the resulting oil was subjected to flash chromatografy (SiO_2, eluent PE/aceton=3/1).
Yield 20.5 g (81%) of the R-benzodioxane as a yellow oil.

Step 3 (scheme i): To a solution of R-benzodioxane (20 g, 81 mmol) in DMF (200 ml) was added KOH (4.56 g, 81 mmol). After cooling the red solution in ice/aceton dimethyl sulfate (23 ml) was added and the reaction mixture was stirred for 1.5 hours at room temperature. Then more KOH (4.56 g, cooling) was added and the mixture was stirred at room temperature for 16 hours. After adding water (700 ml), the product was extracted with ethyl acetate. The ethyl acetate was removed *in vacuo* and the resulting oil was subjected to flash chromatografy (SiO_2, eluent PE/aceton=4/1) yielding R-methoxymethylbenzodioxane (12.3 g, 58%) as a yellow oil. $[\alpha]_D^{25}$= -97° (methanol).

Step 4 (scheme i): To a solution of R- methoxymethylbenzodioxane (5 g, 19 mmol) in ethanol (100 ml) and ethyl acetate (50 ml) was added a catalytic amount of 10% Pd/C and the solution was shaken under atmospheric H_2 pressure at room temperature. After the calculated amount of H_2 was taken up by the reaction mixture, the catalyst was removed by filtration and the filtrate was concentrated *in vacuo.* Yield 3.7 g (100%) of the corresponding anilino-compound.

Step 5 (scheme i): The anilino-compound (4 g, 2 mmol) and BCEA, i.e. $HN(CH_2CH_2Cl)_2.HCl$ (3.7 g , 2 mmol) were dissolved in chlorobenzene (100 ml). The mixture was heated to 150°C for 16 hours, concentrated *in vacuo* and purified by flash chromatografy (SiO_2 , dichloromethane/methanol/ammonium hydroxide=92/7.5/0.5). Yield 3.67 g (68%) of the piperazine a.i.

Example 2: preparation of compound no. 126

The route is described above, i.e. reaction of compound (II) with compound (III). The mesylates of formula (III) were prepared from the corresponding alcohols by standard procedures, *e.g.* with $MsCl/Et_3N$.

A mixture of the piperazine a,i (3,6 g , 13,6 mmol) , the 5-fluoro indole-mesylate (4,1 g , 15,1 mmol), triethylamine (2 ml) and a catalytic amount of KI in CH_3CN (100 ml) was heated under reflux during 18 hours after which the reaction mixture was concentrated *in vacuo* and purified by chromatografy (SiO_2 , dichloromethane/methanol/ammonium hydroxide =92/7.5/0.5). Yield 3,77 of the free base (oil). The free base was dissolved in ethanol and 1 equivalent of fumaric acid in ethanol was added. After removal of the solvent compound no. 126 was obtained (4,3 g, 57%). $[\alpha]_D^{25}$ = -2° (methanol)

Example 3 : preparation of compound b,ii (see scheme ii)

Step 1 (scheme ii): A solution of the aminophenol (37.3 g, 198 mmol), S-lactic acid methyl ester (20 ml) and triphenylphosphine (58 g, 220 mmol) in THF (2000 ml) was cooled in ice/salt (temperature <10°C). Then a solution of azodicarboxic acid ester (DIAD, 43 ml , 218 mmol) in THF (400 ml) was added slowly. After stirring at room temperature for 18 hours the reaction mixture was concentrated *in vacuo* and ethanol (500 ml) and 36% HCl (125 ml) were added to the residue. The mixture was heated to 100°C (development of gas). After cooling the compound was isolated by filtration and washed with 96% ethanol (about 100 ml). Yield 42 g (87%).

Step 2 (scheme ii): This step is similar to step 4 described in scheme i.

Step 3 (scheme ii): This step is similar to step 5 described in scheme i, resulting in the formation of the piperazine b,ii.

Example 4: preparation of compound no. 89

The route is described above, i.e. reaction of compound (II) with compound (III). The reaction is carried out as described in example 2, starting with the piperazine b,ii . Yield 58% of compound no. 89, $[\alpha]_D^{25}$ = -24° (methanol).

Example 5: preparation of coumpound c,iii (see scheme iii)

Step 1 (scheme iii): A solution of the benzomorpholinone (10 g , 41 mmol ; see scheme ii, step 1) and powdered KOH (2.3 g , 41 mmol) in DMF (100 ml) was cooled

in ice (temperature <10°C). After adding 1 equivalent of MeI (2.55 ml, 41 mmol) the reaction mixture was stirred at room temperature for about 1.5 hours and then poured into water. The precipitate was filtered off, washed with water and dried. Yield 10 g (95%) of the NCH_3-compound, mp. 191-192; $[\alpha]_D^{25}$ = +7.5° (in THF)

Step 2 (scheme iii): This step is similar to step 4 described in scheme i.

Step 3 (scheme iii): This step is similar to step 5 described in scheme i, resulting in the formation of the piperazine c,iii.

Example 6 : preparation of compound no. 121

The route is described above, i.e. reaction of compound (II) with compound (III). The reaction is performed as described in example 2, starting with the piperazine c,iii . Yield 44% of compound no. 121, $[\alpha]_D^{25}$ = -28° (methanol).

Example 7: preparation of compound d,iv (see scheme iv)

Step 1 (scheme iv): Pyridine (81ml, 1 mol) was added to a solution of 2-hydroxy-5-chloroaniline (143.5 g, 1 mol) in dry CH_2Cl_2. The mixture was cooled in ice (temperature <10°C) and then a solution of 2-bromo-2-methyl-propionylbromide (163 ml, 1 mol) in CH_2Cl_2 (100 ml) was added slowly. The mixture was stirred at room temperature for 18 hours and was poured into CH_2Cl_2 (5000 ml) and water (2000 ml). The organic layer was washed with water, dried and concentrated *in vacuo* till about 1 litre. The precipitate was filtered off, washed with CH_2Cl_2 and dried. Yield 231 g (79%) of the bromocompound, mp. 172°C.

Step 2 (scheme iv): To a suspension of the bromocompound (60 g , 205 mmol) in water (95 ml) was added slowly under ice cooling concentrated sulfuric acid (7 ml) followed by 70% HNO_3 (16 ml) and stirring was continued for 2 hours at room temperature. After cooling in ice water the precipitate was filtered off, washed with water and purified by chromatografy (SiO_2, methyl t-butylether). Yield 49 g (71%) of the nitrocompound.

Step 3 (scheme iv): To a solution of the nitrocompound (49 g , 145 mmol) in DMF (500ml) was added K_2CO_3. This mixture was heated for one hour at 150°C, then cooled and poured into a mixure water / ethyl acetate.The organic fraction was washed with sodium bicarbonate (5% in water) , HCl (2N) and water respectively. The solvent

was removed *in vacuo* and the residue was purified by flash chromatografy (SiO_2, methyl t-butylether / PE = 1 / 1). Yield 23 g (62%).

Step 4 (scheme iv): This step is similar to step 4 described in scheme i.

Step 5 (scheme iv): This step is similar to step 5 described in scheme i, leading to the formation of the piperazine d,iv.

Example 8: preparation of compound no. 115

The route is described above, i.e. reaction of compound (II) with compound (III). The reaction is performed as described in example 2, starting with the piperazine d,iv . Yield 20% of compound no. 115.

The compounds listed in the following tables have been prepared according to the method of the above examples.

Comp. no	X	m	Y	R_5	R_6	(R7)n	R	Z	A	S_6+ S_7	P	T	Q	Remarks
1	form 2	3	-	H	H	H	2-CH_2OH	-	-	-	-	-	-	S_1=H
2	1	3	C	H	H	H	-	-	-	-	-	-	-	S_1-S_5=H
3	3	3	-	H	H	H	-	O	-	-	-	-	-	S_1=H
4	3	4	-	H	H	H	-	O	-	-	-	-	-	S_1=H
5	3	4	-	H	H	H	-	O	-	-	-	-	-	S_1=H
6	3	3	-	H	CH_3	H	-	O	-	-	-	-	-	S_1=H
7	2	3	-	H	H	H	3-CH_2OH	-	-	-	-	-	-	S_1=H
8	1	3	O	H	H	H	-	-	-	-	-	-	-	S_4=oxo, S_1=S_2=S_3=S_5=H
9	1	3	O	H	H	H	-	-	-	-	-	-	-	S_1-S_5=H
10	4	3	-	H	H	H	-	-	-	-	-		-	S_1=H
11	1	3	C	H	H	H	-	-	-	-	-	-	-	S_1, S_3-S_5=H S_2=CH_3
12	3	3	-	H	-$(CH_2)_3$-		-	O	-	-	-	-	-	S_1=H
13	2	3	-	H	H	H	3-CH_2OH	-	-	-	-	-	-	S_1=H
14	1	3	C	-$(CH_2)_4$		H	-	-	-	-	-	-	-	S_1-S_5=H
15	3	3	-	H	H	5-OCH_3	-	O	-	-	-	-	-	S_1=H
16	1	3	C	CH_3	H	5-Cl	-	-	-	-	-	-	-	S_1-S_5=H
17	3	3	-	CH_3	H	5-Cl	-	O	-	-	-	-	-	S_1=H
18	1	3	C	H	H	5-Br	-	-	-	-	-	-	-	S_1-S_5=H
19	3	3	-	H	H	5-Br	-	O	-	-	-	-	-	S_1=H
20	1	2	C	H	H	H	-	-	-	-	-	-	-	S_1-S_5=H
21	1	3	C	H	H	5-F	-	-	-	-	-	-	-	S_1-S_5=H
22	3	3	-	H	H	5-F	-	O	-	-	-	-	-	S_1=H
23	3	3	-	H	H	H	-	CH_2	-	-	-	-	-	S_1=H
24	5	3	-	H	H	H	-	-	O	-	-	-	-	S_1=H; position 8
25	1	3	C	H	H	7-Cl	-	-	-	-	-	-	-	S_1-S_5=H

5

Comp. no	X	m	Y	R_5	R_6	(R7)n	R	Z	A	S_8+S_7	P	T	Q	Remarks
26	form 3	3	-	H	H	7-F	-	O	-	-	-	-	-	S_1=H
27	1	3	C	H	H	7-F	-	-	-	-	-	-	-	S_1-S_5=H
28	3	3	-	H	H	7-Cl	-	O	-	-	-	-	-	S_1=H
29	3	3	-	H	H	7-CH_3	-	O	-	-	-	-	-	S_1=H
30	2	3	-	H	H	H	2-CH_2OCH_3	-	-	-	-	-	-	S_1=H
31	7	3	-	H	H	H	-	-	-	-	N	CH_2	CH_2	S_1=H
32	1	3	C	H	H	6-Cl	-	-	-	-	-	-	-	S_1-S_5=H
33	3	3	-	H	H	6-Cl	-	O	-	-	-	-	-	S_1=H
34	3	3	-	H	H	5-CN	-	O	-	-	-	-	-	S_1=H
35	1	3	C	H	H	5-CN	-	-	-	-	-	-	-	S_1-S_5=H
36	1	3	C	H	H	4-Cl	-	-	-	-	-	-	-	S_1-S_5=H
37	3	3	-	H	H	4-Cl	-	O	-	-	-	-	-	S_1=H
38	1	6	C	H	H	H	-	-	-	-	-	-	-	S_1-S_5=H
39	1	5	C	H	H	H	-	-	-	-	-	-	-	S_1-S_5=H
40	1	3	C	H	H	H	-	-	-	-	-	-	-	S_1-S_4=H S_5=CH_3
41	1	3	S	H	H	H	-	-	-	-	-	-	-	S_4=oxo, S_1-S_3=S_5=H
42	6	3	-	H	H	H	-	-	-	oxo	-	-	-	S_1=H
43	1	3	S	H	H	H	-	-	-	-	-	-	-	S_1-S_5=H
44	6	3	-	H	H	H	-	-	-	H_2	-	-	-	S_1=H
45	1	4	C	H	H	H	-	-	-	-	-	-	-	S_1-S_5=H
46	1	3	C	H	H	6-F	-	-	-	-	-		-	S_1-S_5=H
47	3	3	-	H	H	6-F	-	O	-	-	-	-	-	S_1=H
48	7	3	-	H	H	H	-	-	-	-	N	CH	NH	S_1=H
49	1	3	O	H	H	H	-	-	-	-	-	-	-	S_4=oxo, S_2=CH_3, S_1=S_3=S_5=H
50	1	3	C	H	H	H	-	-	-	-	-	-	-	S_4=oxo, S_1-S_3=S_5=H

Comp. no	X	m	Y	R_5	R_6	(R7)n	R	Z	A	S_6+S_7	P	T	Q	Remarks
51	form 3	3	-	H	C_2H_5	5-CN	-	O	-	-	-	-	-	S_1=H
52	3	3	-	H	H	H	-	NH	-	-	-	-	-	S_1=H
53	7	3	-	H	H	H	-	-	-	-	N	$C(CH_3)$	NH	S_1=H
54	7	3	-	H	H	H	-	-	-	-	NH	N	CH	S_1=H
55	7	3	-	H	H	H	-	-	-	-	N	N	NH	S_1=H
56	1	3	C	H	H	4-F	-	-	-	-	-	-	-	S_1-S_5=H
57	3	3	-	H	H	4-F	-	O	-	-	-	-	-	S_1=H
58	1	3	C	H	H	7-Br	-	-	-	-	-	-	-	S_1-S_5=H
59	3	3	-	H	H	7-Br	-	O	-	-	-	-	-	S_1=H
60	1	3	O	H	H	H	-	-	-	-	-	-	-	S_4=oxo, S_1=7-Cl, S_2=S_3=S_5=H
61	2	3	-	H	H	5-F	2-CH_2OCH_3	-	-	-	-	-	-	S_1=H
62	1	3	C	H	H	5,7-F_2	-	-	-	-	-	-	-	S_1-S_5=H
63	3	3	-	H	H	5,7-F_2	-	O	-	-	-	-	-	S_1=H
64	2	3	-	H	H	7-F	2-CH_2OCH_3	-	-	-	-	-	-	S_1=H
65	5	3	-	H	H	H	-	-	NH	-	-	-	-	S_1=H; position 5
66	5	3	-	H	H	5-F	-	-	NH	-	-	-	-	S_1=H; position 5
67	5	3	-	H	H	7-F	-	-	NH	-	-	-	-	S_1=H; position 5
68	2	3	-	H	H	H	3-CH_2OCH_3	-	-	-	-	-	-	S_1=H
69	2	3	-	H	H	H	2-CH_2OCH_3	-	-	-	-	-	-	S_1=H
70	2	3	-	H	H	5-F	2-CH_2OCH_3	-	-	-	-	-	-	S_1=H
71	2	3	-	H	H	5-F	3-CH_2OCH_3	-	-	-	-	-	-	S_1=H
72	2	3	-	H	H	7-F	3-CH_2OCH_3	-	-	-	-	-	-	S_1=H
73	2	3	-	H	H	7-F	2-CH_2OCH_3	-	-	-	-	-	-	S_1=H
74	1	3	S	H	H	5-F	-	-	-	-	-	-	-	S_4=oxo, S_1-S_3=S_5=H
75	2	3	-	H	H	H	3-$CH_2OC_3H_7$	-	-	-	-	-	-	S_1=H

Comp. no	X	m	Y	R_5	R_6	(R7) n	R	Z	A	S_6+S_7	P	T	Q	Remarks
76	form.2	3	-	H	H	5-F	3-$CH_2OC_3H_7$	-	-	-	-	-	-	S_1=H
77	2	3	-	H	H	H	3-$CH_2OCH_2C{\equiv}CH$	-	-	-	-	-	-	S_1=H
78	2	3	-	H	H	5-F	3-$CH_2OCH_2C{\equiv}CH$	-	-	-	-	-	-	S_1=H
79	2	3	-	H	H	7-F	3-$CH_2OCH_2C{\equiv}CH$	-	-	-	-	-	-	S_1=H
80	2	3	-	H	H	H	3-$CH_2OCH_2CH_2OCH_3$	-	-	-	-	-	-	S_1=H
81	2	3	-	H	H	5-F	3-$CH_2OCH_2CH_2OCH_3$	-	-	-	-	-	-	S_1=H
82	2	3	-	H	H	7-F	3-$CH_2OCH_2CH_2OCH_3$	-	-	-	-	-	-	S_1=H
83	1	3	S	H	H	5-F	-	-	-	-	-	-	-	S_1=H
84	1	3	S	H	H	H	-	-	-	-	-	-	-	S_1-S_5=H
85	1	3	S	H	H	H	-	-	-	-	-	-	-	S_2=CH_3,S_1=S_3-S_5=H
86	7	3	-	H	H	H	-	-	-	-	-	-	-	S_4=oxo, S_2=CH_3, S_1=S_3=S_5=H
87	1	3	O	H	H	H	-	-	-	-	N	CH	S	S_1=H
88	1	3	O	H	H	H	-	-	-	-	-	-	-	S_4=oxo, S_2=CH_3, S_1=S_3=S_5=H
89	1	3	O	H	H	5-F	-	-	-	-	-	-	-	S_4=oxo, S_2=CH_3, S_1=S_3=S_5=H
90	1	3	O	H	H	5-F	-	-	-	-	-	-	-	S_4=oxo, S_2=CH_3, S_1=S_3=S_5=H
91	1	3	O	H	H	7-F	-	-	-	-	-	-	-	S_4=oxo, S_2=CH_3, S_1=S_3=S_5=H
92	1	3	O	H	H	7-F	-	-	-	-	-	-	-	S_4=oxo, S_2=CH_3, S_1=S_3=S_5=H
93	1	3	O	H	H	H	-	-	-	-	-	-	-	S_4=oxo, S_2=CH_3, S_1=S_3=S_5=H
94	1	3	O	H	H	5-F	-	-	-	-	-	-	-	S_4=oxo, S_2= phenyl, S_1=S_3=S_5=H
95	1	3	O	H	H	7-F	-	-	-	-	-	-	-	S_4=oxo, S_2= phenyl, S_1=S_3=S_5=H
96	2	3	-	H	H	H	3-$CH_2OCH_2CH{=}CH_2$	-	-	-	-	-	-	S_4=oxo, S_2= phenyl, S_1=S_3=S_5=H
97	2	3	-	H	H	5-F	3-$CH_2OCH_2CH{=}CH_2$	-	-	-	-	-	-	S_1=H
98	2	3	-	H	H	7-F	3-$CH_2OCH_2CH{=}CH_2$	-	-	-	-	-	-	S_1=H
99	2	3	-	H	H	H	2-$CH_2OCH_2C{\equiv}CH$	-	-	-	-	-	-	S_1=H
100	2	3	-	H	H	5-F	2-$CH_2OCH_2C{\equiv}CH$	-	-	-	-	-	-	S_1=H

Comp. no	X	m	Y	R_5	R_6	(R7)n	R	Z	A	S_6+S_7	P	T	Q	Remarks
101	form. 2	3	-	H	H	7-F	2-$CH_2OCH_2C{\equiv}CH$	-	-	-	-	-	-	S_1=H
102	1	3	O	H	H	H	-	-	-	-	-	-	-	S_4=oxo, S_2=C_3H_7, S_1=S_3=S_5=H
103	1	3	O	H	H	5-F	-	-	-	-	-	-	-	S_4=oxo, S_2=C_3H_7, S_1=S_3=S_5=H
104	1	3	O	H	H	7-F	-	-	-	-	-	-	-	S_4=oxo, S_2=C_3H_7, S_1=S_3=S_5=H
105	1	3	O	H	H	H	-	-	-	-	-	-	-	S_4=oxo, S_2=S_5=CH_3, S_1=S_3=H
106	1	3	O	H	H	5-F	-	-	-	-	-	-	-	S_4=oxo, S_2=S_5=CH_3, S_1=S_3=H
107	1	3	O	H	H	7-F	-	-	-	-	-	-	-	S_4=oxo, S_2=S_5=CH_3, S_1=S_3=H
108	1	3	O	H	H	H	-	-	-	-	-	-	-	S_4=oxo, S_2=benzyl, S_1=S_3=S_5=H
109	1	3	O	H	H	5-F	-	-	-	-	-	-	-	S_4=oxo, S_2=benzyl, S_1=S_3=S_5=H
110	1	3	O	H	H	7-F	-	-	-	-	-	-	-	S_4=oxo, S_2=benzyl, S_1=S_3=S_5=H
111	2	3	-	H	H	H	3-$CH_2OCH_2C{\equiv}CCH_3$	-	-	-	-	-	-	S_1=H
112	2	3	-	H	H	H	2-$CH_2OCH_2C{\equiv}CCH_3$	-	-	-	-	-	-	S_1=H
113	2	3	-	H	H	5-F	2-$CH_2OCH_2C{\equiv}CCH_3$	-	-	-	-	-	-	S_1=H
114	1	3	O	H	H	H	-	-	-	-	-	-	-	S_4=oxo, S_2=S_3=CH_3, S_1=S_5=H
115	1	3	O	H	H	5-F	-	-	-	-	-	-	-	S_4=oxo, S_2=S_3=CH_3, S_1=S_5=H
116	2	3	-	H	H	H	3-CH_2OCH_3	-	-	-	-	-	-	S_1=H
117	2	3	-	H	H	5-F	3-CH_2OCH_3	-	-	-	-	-	-	S_1=H
118	2	3	-	H	H	5-F	3-CH_2OCH_3	-	-	-	-	-	-	S_1=H
119	2	3	-	H	H	H	3-CH_2OCH_3	-	-	-	-	-	-	S_1=H
120	1	3	O	H	H	H	-	-	-	-	-	-	-	S_4=oxo, S_2=S_5=CH_3,S_1=S_3=H
121	1	3	O	H	H	5-F	-	-	-	-	-	-	-	S_4=oxo, S_2=S_5=CH_3,S_1=S_3=H
122	1	3	O	H	H	5-F	-	-	-	-	-	-	-	S_4=oxo, S_2=S_5=CH_3,S_1=S_3=H
123	1	3	O	H	H	H	-	-	-	-	-	-	-	S_4=oxo, S_2=S_5=CH_3,S_1=S_3=H
124	1	3	O	H	H	5-F	-	-	-	-	-	-	-	S_4=oxo, S_1=7-Cl, S_2=S_3=S_6=CH_3
125	1	3	O	H	H	5-F	-	-	-	-	-	-	-	S_4=oxo, S_1=H,S_2=S_3=S_5=CH_3
126	2	3	-	H	H	5-F	3-CH_2OCH_3	-	-	-	-	-	-	S_1=H

Comp. no	Salt or free base	MP(°C)	$[\alpha]_D^{25}$ (in methanol)
1	fumarate	192-4	-
2	2-HCl	239-41	-
3	free base	203-4	-
4	"	170-1	-
5	3.fumarate	98	-
6	free base	175-6	-
7	4/3. fumarate	140-3	-
8	free base	189-90	-
9	fumarate	200-1	-
10	3/2. fumarate	190-1	-
11	½ .fumarate	210-2 (dec.)	-
12	free base	165-7	-
13	free base	70-1	-
14	fumarate	208	-
15	free base	amorph	-
16	2. fumarate	amorph	-
17	free base	amorph	-
18	fumarate	>225 (dec.)	-
19	fumarate	>170 (dec.)	-
20	free base	amorph	-
21	½. fumarate	>245 (dec)	-
22	½. fumarate	>165 glass)	-
23	free base	176-7	-
24	free base	amorph	-
25	½. fumarate	amorph	-
26	¾. fumarate	amorph	-
27	½. fumarate	> 240 (dec)	-
28	4/5. fumarate	amorph	-
29	"	amorph	-
30	3/2. fumarate	glass	-
31	5/4. fumarate	188-190	-
32	½. fumarate	>230 (dec)	-
33	fumarate	amorph	-
34	fumarate	150-2	-
35	½. fumarate	247-8 (dec)	-
36	½. fumarate	>240 (dec)	-
37	fumarate	amorph	-
38	HCl	amorph	-
39	HCl	amorph	-
40	HCl	220-4	-
41	HCl	>250 (dec)	-
42	½. fumarate	214-7(dec)	-
43	½. fumarate	240-3	-
44	½. fumarate	220-2(dec)	-
45	HCl	amorph	-
46	fumarate	223-5	-
47	2/3. fumarate	200-2	-
48	free base	glass	-
49	free base	196-7	-
50	free base	181-2	-

Comp. no	Salt or free base	MP(°C)	$[\alpha]_D^{25}$ (in methanol)
51	½. fumarate	138.5-41	-
52	free base	190-5(dec)	-
53	free base	glass	-
54	free base	glass	-
55	free base	glass	-
56	½. fumarate	185-6	-
57	fumarate	210-1(dec)	-
58	2. fumarate	amorph	-
59	free base	amorph	-
60	½. fumarate	>250	-
61	fumarate	glass	-
62	½. fumarate	245-7	-
63	3/2.fumarate	175-8	-
64	fumarate	glass	-
65	free base	220-4(dec)	-
66	free base	234-6(dec)	-
67	free base	>280	-
68	HCl	glass	-
69	fumarate	glass	+28 (free base), R-conf.
70	fumarate	glass	+28 (free base), R-conf.
71	fumarate	glass	-
72	fumarate	glass	-
73	fumarate	glass	+25 (free base), R-conf.
74	free base	212.5-14.5	-
75	fumarate	glass	-
76	fumarate	glass	-
77	fumarate	glass	-
78	fumarate	glass	-
79	fumarate	glass	-
80	fumarate	glass	-
81	fumarate	glass	-
82	fumarate	glass	-
83	fumarate	amorph	-
84	free base	amorph	-
85	free base	amorph	-
86	½. fumarate	218-20	-
87	free base	glass	-26 R-conf.
88	free base	glass	+27 S-conf.
89	free base	glass	-24 R-conf.
90	free base	glass	+24 S-conf.
91	free base	184-5	-25 R-conf.
92	free base	181-3	+25 S-conf.
93	free base	glass	-
94	free base	glass	-
95	free base	glass	-
96	free base	70-3	-
97	free base	73-5	-
98	fumarate	glass	-
99	fumarate	glass	+39 (free base), R-conf.
100	fumarat	glass	+36 (free base), R-conf.

Comp. no	Salt or free base	MP(°C)	$[\alpha]_D^{25}$ (in methanol)
101	fumarate	glass	+37 (free base), R-conf.
102	free bas	158-60	-
103	free base	181-2	-
104	free base	174-6	-
105	free base	glass	-
106	free base	glass	-
107	free base	glass	-
108	free base	glass	-
109	free base	207-10(dec)	-
110	free base	197-9(dec)	-
111	fumarate	glass	-
112	fumarate	glass	+31 (free base), R-conf
113	fumarate	glass	+31 (free base), R-conf
114	free base	191-4	-
115	free base	190-2	-
116	free base	amorph	0 S-conf.
117	fumarate	amorph	S-conf.
118	free base	amorph	R-conf.
119	free base	amorph	0 R-conf.
120	free base	amorph	-31 R-conf.
121	free base	amorph	-28 R-conf.
122	free base	amorph	+28 S-conf.
123	free base	amorph	+32 S-conf.
124	free base	amorph	-
125	free base	amorph	-
126	fumarate	amorph	-2 R-conf.

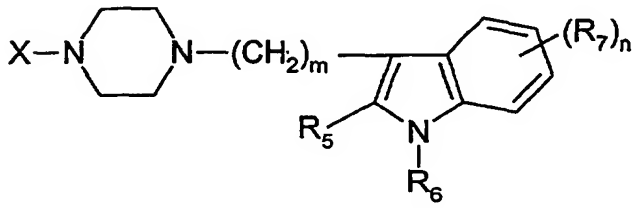
5

10

Claims

1. The invention relates to a group of novel phenylpiperazine derivatives of the formula

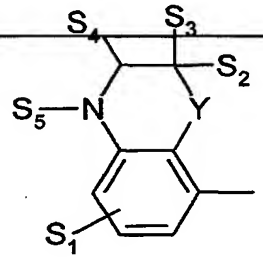
(I):



(I)

wherein:

- X is 1) a group of the formula

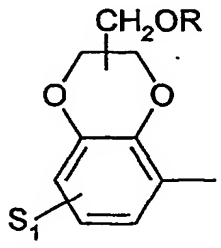


(1)

wherein

- S_1 is hydrogen or halogen,
- S_2 and S_3 are independently hydrogen, alkyl (1-6C), phenyl or benzyl,
- S_4 represents two hydrogen atoms or an oxo group,
- S_5 is H or alkyl (1-4C), and
- Y is C, O or S,

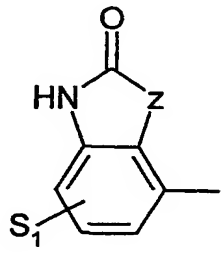
or 2) a group of the formula



(2)

wherein S_1 has the above meaning and R is H, alkyl (1-4C), alkoxyalkyl (2-6C), alkenyl (2-4C) or alkynyl (2-4C),

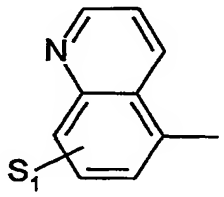
or 3) a group of the formula



(3)

wherein S_1 has the above meaning and Z is C, O or N,

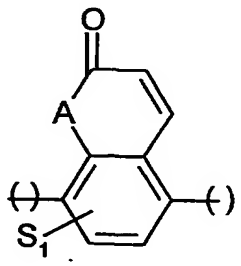
or 4) a group of the formula



(4)

wherein S_1 has the above meaning,

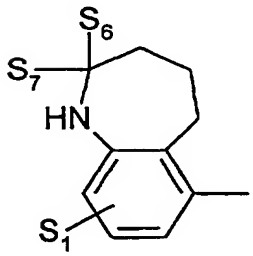
or 5) a group of the formula



(5)

wherein S_1 has the above meaning and A is O or N, linked to the piperazine ring with position 5 or 8,

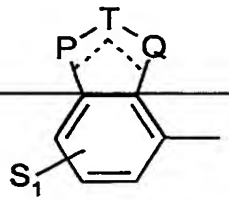
or 6) a group of the formula



(6)

wherein S_1 has the above meaning and S_6 and S_7 represent hydrogen atoms or an oxo group,

or 7) a group of the formula



(7)

wherein one of the dotted lines can represent a double bond, S_1 has the above meaning, and

P=T=Q=nitrogen

or P=T=nitrogen and Q=C

or P=Q=nitrogen and T=C or C-CH_3

or P=nitrogen, and T and Q are carbon

or P=nitrogen, T is carbon and Q is sulphur

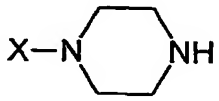
- m has the value 2 to 6;
- n has the value 0-2;
- R_5 and R_6 are independently H or alkyl (1-3C); or R_5+R_6 represent a group $-(CH_2)-_p$ wherein p has the value 3-5, and
- R_7 is alkyl (1-3C), alkoxy (1-3C), halogen or cyano; or R_6+R_7 represent a group $-(CH_2)_q$ wherein q has the value 2-4,

and salts thereof.

2. A compound as claimed in claim 1, wherein X represents a group of the formula (1), (2) or (3), wherein the symbols have the meanings given in claim 1.

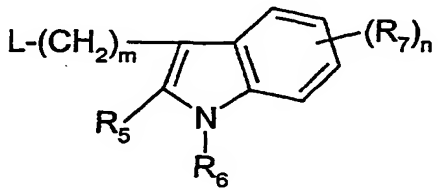
3. A compound as claimed in claim 1, wherein X is the group having formula (I), wherein $S_1=S_3=S_5=H$, S_4=oxo and $S_2=CH_3$, m is 3, $R_5=R_6=H$, n is 0 or 1, and R_7 is fluoro, and salts thereof.

4. Method for the preparation of compounds as claimed in claim 1, characterised in that a compound having formula (II)



(II)

is reacted under basic conditions with a compound having formula (III)



(III)

in which formulae the symbols having the meanings given in claim 1, and L is a so-called leaving group.

5. A pharmaceutical composition containing at least one compound as claimed in claim 1 as an active component.

6. A method of preparing a composition as claimed in claim 5, characterised in that a compound of claim 1 is brought into a form suitable for administration.

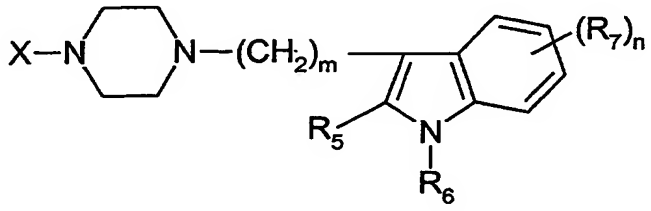
7. A method of treating CNS disorders, characterised in that a compound as claimed in claim 1 is used.

(67)

ABSTRACT

The invention relates to a novel group of phenylpiperazines having interesting pharmacological properties.

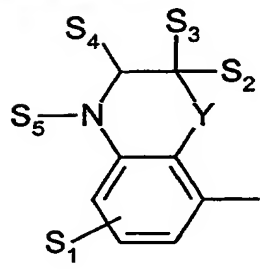
The invention relates to a group of novel phenylpiperazine derivatives of the formula (I):



(I)

wherein:

- X is 1) a group of the formula

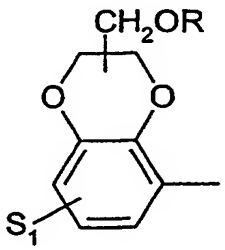


(1)

wherein

- S_1 is hydrogen or halogen,
- S_2 and S_3 are independently hydrogen, alkyl (1-6C), phenyl or benzyl,
- S_4 represents two hydrogen atoms or an oxo group,
- S_5 is H or alkyl (1-4C), and
- Y is C, O or S,

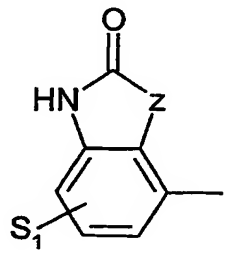
or 2) a group of the formula



(2)

wherein S_1 has the above meaning and R is H, alkyl (1-4C), alkoxyalkyl (2-6C), alkenyl (2-4C) or alkynyl (2-4C),

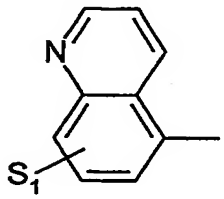
or 3) a group of the formula



(3)

wherein S_1 has the above meaning and Z is C, O or N,

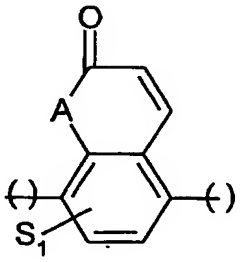
or 4) a group of the formula



(4)

wherein S_1 has the above meaning,

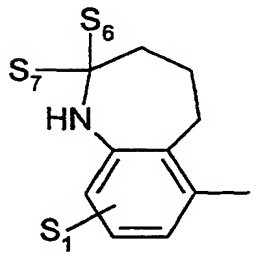
or 5) a group of the formula



(5)

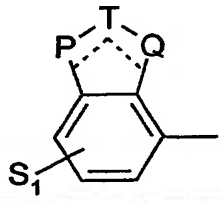
wherein S_1 has the above meaning and A is O or N, linked to the piperazine ring with position 5 or 8,

or 6) a group of th formula



(6)

wherein S_1 has the above meaning and S_6 and S_7 represent hydrogen atoms or an oxo group,



(7)

or 7) a group of the formula

wherein one of the dotted lines can represent a double bond, S_1 has the above meaning, and

P=T=Q=nitrogen

or P=T=nitrogen and Q=C

or P=Q=nitrogen and T=C or C-CH_3

or P=nitrogen, and T and Q are carbon

or P=nitrogen, T is carbon and Q is sulphur

- m has the value 2 to 6;
- n has the value 0-2;
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- R_7 is alkyl (1-3C), alkoxy (1-3C), halogen or cyano; or R_6+R_7 represent a group $-(CH_2)_q$ wherein q has the value 2-4,

and salts thereof.